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Mathematical Models for Assessment of Long-Term Persistence of Antibodies After Vaccination With Two Inactivated Hepatitis A Vaccines

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Very few studies with inactivated hepatitis A vaccines were designed for long-term follow-up of antibody persistence. Based on the serological data from these vaccine trials, mathematical models were developed to predict the decrease of anti-hepatitis A virus (anti-HAV) antibodies after vaccination. This study was designed to compare Avaxim (0–6 months) to Havrix 720 (0–1–6 months). In this paper, both groups of vaccinees are described considering the age, gender, and weight of the subjects at enrollment. For mathematical modelling, two different approaches were used: one starting the calculations from the geometric mean titres (GMTs) at each point in time, the other basing the calculations on individual anti-HAV titres. Both vaccines are very immunogenic, although Avaxim shows a higher GMT at each point in time. When these data are used in mathematical models to predict the persistence of anti-HAV antibodies, both vaccines (Avaxim and Havrix 720) show similar long-term antibody kinetics. Antibody levels $\geq$ 20 mIU/ml are estimated to last on average for at least 10 years after completion of the full vaccination course. Ten years after the full course, approximately 53% of subjects are estimated to have antibody levels $\geq$ 20 mIU/ml. At 15 years, these levels will be maintained by about 34% of vaccinees. Avaxim and Havrix 720 show a similar long-term profile of persistence of anti-HAV. A mathematical model based on GMTs appeared to give equivalent results to a model based on individual serological data. The GMT method is easier to apply than the individual based method. However, the advantage of the latter method is the possibility of calculating confidence limits for the predicted values and making estimates of the percentage of subjects having a certain level of antibody titres at a certain time. ***J. Med. Virol. 60:1–7, 2000.***

KEY WORDS: mathematical models; antibody persistence; long-term immunogenicity

INTRODUCTION

Hepatitis A virus (HAV) causes acute inflammation of the liver. Several inactivated vaccines against hepatitis A infection have been developed and are now available in an increasing number of countries worldwide. These vaccines have been shown to be safe and highly immunogenic. As for other vaccines (hepatitis B, diphtheria, rabies vaccines, etc.) [Simonsen et al., 1996; West and Calandra, 1996; Strady et al., 1998], attention has now turned to the evaluation of the long-term persistence and kinetics of antibodies induced by hepatitis A vaccines, in order to document better the need for additional booster immunisations.

As the severity of hepatitis A infection increases with age [Hadler and McFarland, 1986; Centers for Disease Control and Prevention, 1996], it is important to immunise with vaccines that will confer durable protection, to avoid creating a pool of susceptible older subjects. Indeed, if hepatitis A vaccine were to have a limited duration of protection, infection could occur at an older age and immunisation could convert an otherwise asymptomatic childhood infection into a symptomatic disease upon exposure later in life.

Persistence of antibodies after immunisation can be determined only by continued observation over time. Some clinical trials with hepatitis A vaccines were re-

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ported on long-term follow-up [Berger and Just, 1992; Van Damme et al., 1994; Wiens et al., 1996; Bovier et al., 1997; Goilav et al., 1997; Maiwald et al., 1997; Totos et al., 1997; Wiedermann et al., 1997]. Using the serological data from some of these vaccine trials, mathematical models have been developed to predict the decrease of anti-HAV antibodies after booster vaccination. Further follow-up of these vaccine trials should help substantiate the validity or the robustness of these mathematical models.

The data from a vaccine trial with long-term antibody persistence data on two inactivated hepatitis A vaccines are described. These data were used retrospectively in two mathematical models developed previously [Van Damme et al., 1994; Wiens et al., 1996], to test their suitability to predict the duration of antibody persistence.

MATERIALS AND METHODS

The vaccines used in this clinical study were Avaxim (Pasteur Mérieux Connaught, Lyon, France) and Havrix 720 (SmithKline Beecham Biologicals, Rixensart, Belgium). Avaxim consists of 160 antigen units of HAV per 0.5-ml dose [Vidor et al., 1996] and Havrix 720 is formulated to contain not less than 720 Elisa units per 1.0-ml dose [Peetermans, 1992].

In this clinical trial, Avaxim (vaccination schedule: 0–6 months) was compared to Havrix 720 (vaccination schedule: 0–1–6 months) and the results of the first part of the study until 1 month post-booster were reported previously [Goilav et al., 1995]. A yearly follow-up of antibody persistence was also performed for 2 consecutive years, and the results from the first year follow-up have been published [Goilav et al., 1997].

All data sets covering the period from 1 month post-booster (week 28), 1 year post-booster (week 76), and 2 years post-booster (week 128) were submitted by the Biometry Department of Pasteur Mérieux Connaught France to the Centre for the Evaluation of Vaccination, Epidemiology and Community Medicine, University of Antwerp where they were reviewed and cleaned (see below), to retain comparable data sets. To test the robustness and the predictability of the models, the dataset covering the year 3 post-booster period (week 180) was compared subsequently with the predicted values inferred from the previous analysis.

Subjects who were seropositive at the start of the study or who failed to be compliant with the exact vaccination schedule (i.e., booster dose given at week 24 ± 1 week after the first trial vaccination) have been excluded from the analysis. Those subjects who did not have a blood sample taken 4 ± 1 weeks after the booster dose, or who missed one of the annual follow-up visits have also been excluded. Finally, subjects with an anti-HAV antibody titre that increased over time (week 128 ≥ week 76 or week 76 ≥ week 28) were excluded from the analysis, as a negative decline rate was considered clinically irrelevant.

Antibody titres were measured by the BARC Laboratories (Ghent, Belgium) by modified radioimmunoassay (mRIA) (HAVAB, Abbott, Chicago, IL) with a cut-off value for detection of 10 mIU/ml [Miller et al., 1993]. Seroconversion was defined as a rise in anti-HAV from less than 20 mIU/ml to 20 mIU/ml or more.

TABLE I. Demographic Characteristics at Enrollment and Descriptive Results of Subjects Given Either Avaxim™ (0–6 Months) or Havrix 720™ (0–1–6 Months)

Vaccine	N	Age Mean (range)	M/V Ratio	Weight Mean (range)
AVAXIM	129	29.2 (18.0–54.5)	48/81	66.5 (43.0–100.0)
HAVRIX 720	145	28.3 (18.1–55.5)	53/92	65.1 (37.5–95.0)

M, male; F, female; GMT, geometric mean titre; CI, confidence interval.

For the analysis, the remaining subjects were first described for different variables such as gender, age, and weight at time of trial enrollment; GMTs; number of seroconverters; and seroconversion rates at each time point available. Second, the antibody titres were log-transformed to obtain normally distributed data, and an analysis of variance was used to assess the effect of the gender, age and weight on these log-transformed serological data ($\log_{10}$[titre]). Third, the applicability of the existing formulae [Van Damme et al., 1994; Wiens et al., 1996] for mathematical modelling of anti-HAV antibody persistence to the different data sets was verified by interpolation. After adapting the formulae accordingly, calculations of long-term persistence of anti-HAV antibodies were performed for each of the groups. Fourth, a predicted value for the GMT in the two groups for the year 3 post-booster was estimated, and then compared with the real observed values from this trial.

Data were processed using Statistica 5.0 for Windows (StatSoft Inc., © 1996) and Microsoft Excel 7.0 (Microsoft Corporation, © 1983–1995). For statistical analysis, the chi-square test was applied to compare proportions and Student's t-test to compare mean values. A probability $P < .05$ was considered to be statistically significant.

RESULTS

The two groups were comparable for gender, age, and weight at inclusion. Tables I and II show GMT values at weeks 24, 28, 76, and 128 per study group. Seroconversion rates (SC%) are not presented, because 100% of the subjects remained above the 20 mIU/ml level at all time points.

GMT values at each time point for the two vaccine groups are shown in Figure 1. Both vaccines (Avaxim and Havrix 720) proved to be very immunogenic. Because no blood sampling was done during the study between 4 weeks and 1 year after the administration of the booster dose, this graph does not show very clearly the typical distinction between the first phase of rapid antibody decrease after the antibody peak at week 28 and the second phase of a constant, slow decrease of antibody titres, as has been reported previously [Van Damme et al., 1994; Wiens et al., 1996; Bovier et al., 1997; Totos et al., 1997; Wiedermann et al., 1997].

TABLE II. Descriptive Results of Subjects Given Either Avaxim (0–6 months) or Havrix 720 (0–1–6 Months)

Vaccine	Week 24 Booster GMT (95% CI)	Week 28 1 month post-booster GMT (95% CI)	Week 76 1 year post-booster GMT (95% CI)	Week 128 2 years post-booster GMT (95% CI)
AVAXIM	270 (225–323)	3996 (3357–4756)	1359 (1116–1655)	832 (692–1000)
HAVRIX 720	222 (189–260)	3076 (2582–3665)	1051 (877–1260)	666 (558–796)

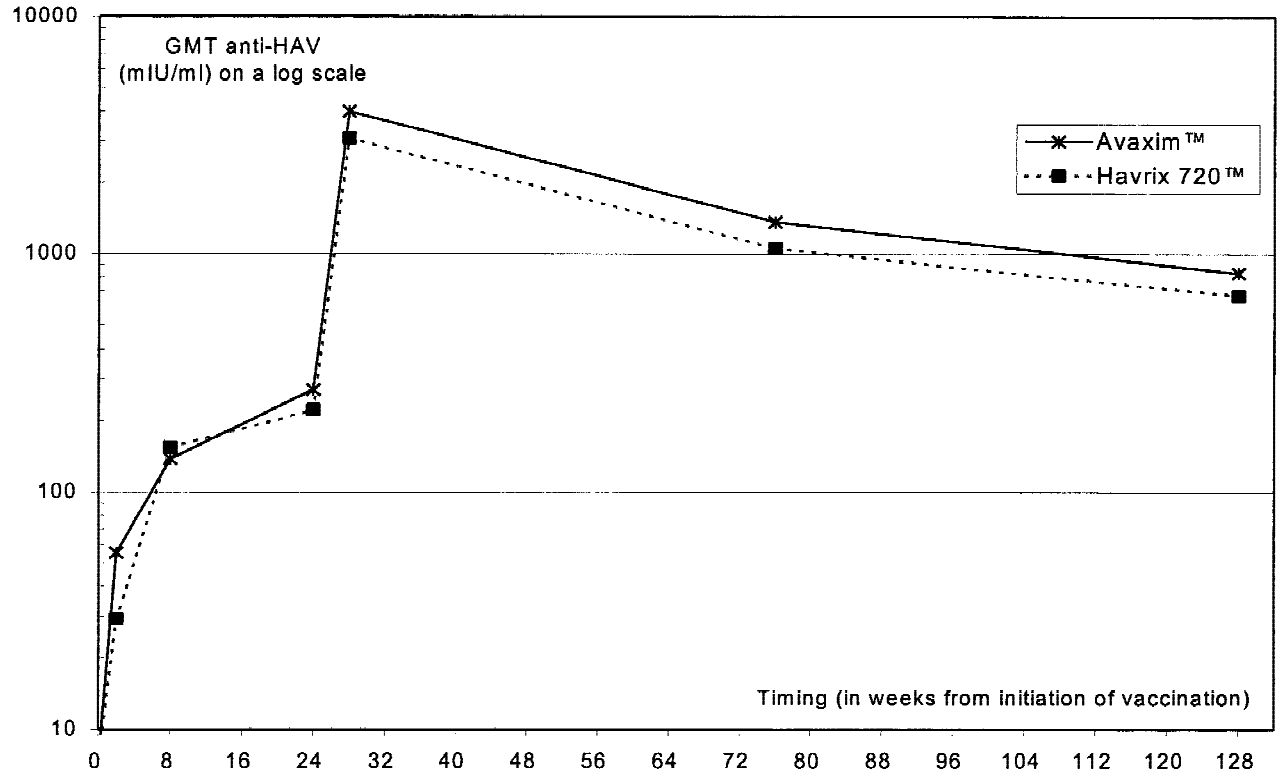

Fig. 1. Long-term persistence of anti-hepatitis A virus (anti-HAV) antibodies in subjects given either Avaxim (0–6 months) or Havrix 720 (0–1–6 months). Geometric mean titres (GMTs) are plotted on a logarithmic scale.

Modelling

Different methods of modelling have been described previously. Van Damme et al. [1994] developed a mathematical formula for the slow decrease rate (linear decrease on a log-linear scale), whereas Wiedermann et al. [1997] developed a more complex formula to describe the rapid and the slow decrease rate in a single model. These two methods were based on the GMT values at each point in time. Others have used a similar mathematical formula, based on calculations using individual data [Wiens et al., 1996; Bovier et al., 1997].

To obtain general conclusions for this analysis, both methods of calculation were applied to the same data set. First, the duration of antibody persistence was calculated based on GMT values, using the GMTs of week 76 and week 128 as a measure of the constant annual slow decrease. Second, we investigated whether the same results would be obtained by calculating both the slow decrease rate and the duration of antibody persistence based on the individual data.

Modelling Based on GMTs

Our starting point was the formula (1) developed by Van Damme et al. [1994]:

$$y = \mathrm{GMT}_{12} * [1 - \delta]^{(x/12)-1} \quad (1)$$

GMT_{12} = Geometric Mean Titre 12 months after first dose
x = number of months after first vaccination, with $x > 12$
δ = annual decline rate for the slow decrease phase

The annual decline rate (δ) was calculated by transposing Eq. (1) to

$$\log_{10}(1 - \delta) = \frac{\log_{10}(\mathrm{GMT}_{128}) - \log_{10}(\mathrm{GMT}_{76})}{\left(\frac{x}{12}\right) - 1} \quad (2)$$

GMT_{76} = Geometric Mean Titre 76 weeks after first dose
GMT_{128} = Geometric Mean Titre 128 weeks after first dose
where $x/12$ = number of years after first dose with 128 weeks being considered as 2.5 years.

The calculated annual decline rate for the slow phase was thus found to be 38.8% and 36.6% for Avaxim and Havrix 720, respectively. With the subsequently calculated values for δ, Eq. (2) was adapted to allow calculation of the number of years ($x/12$) before the GMT in each group would reach 20 mIU/ml, which is considered to be the level of seroconversion [Miller et al., 1993]. Thus, $x/12$ was calculated as follows:

$$\frac{x}{12} = \frac{\log_{10}(20) - \log_{10}(GMT_{76})}{\log_{10}(1-\delta)} + 1 \quad (3)$$

where 20 = the anti-HAV level for seroconversion
$x/12$ = the number of years after the first dose, before GMT = 20 mIU/ml.

By doing so, the duration of antibody persistence ≥ 20 mIU/ml in this trial was found to be 10.1 years for Avaxim and 10.2 years for Havrix 720.

Modelling Based on Individual Data

Here, the following formula by Wiens et al. [1996] was used:

$$y_x = Z_n * [1-\delta]^{(x-n/m-n)} \quad (4)$$

y_x = individual titre at time x
Z_n = individual titre at time n
m and n are a number of months after first dose defining an interval for which titres are known
x = the number of months after the first dose, when titre y_x will be reached
δ = annual decline rate.

The annual slow decrease rate (δ) was calculated for each subject individually. In these calculations, the following parameter values were used: $m = 32$, $n = 19$, $x = 32$, and Z_n = the individual titre at week 76. By doing so, the mean annual decrease rate (slow phase) for Avaxim was 35.3% (95% confidence interval [CI]: 31.8–38.8%), compared with 33.3% (95% CI: 30.2–36.3%) for Havrix 720, based on the following equation:

$$\log_{10}(1-\delta) = \frac{\log_{10}(titer_{128}) - \log_{10}(titer_{76})}{\frac{x-n}{m-n}} \quad (5)$$

with $(x-n)/(m-n) = (32-19)/(32-19) = 1$.

With these calculated individual values for δ, the number of years (x) before an individual reached the seroconversion level of 20 mIU/ml was calculated. For these individual values for x, the means with their 95% CI were 29.7 years (95% CI: 17.4–42.0 years) for Avaxim, compared with 45.0 years (95% CI: 3.0–86.9 years) for the subjects vaccinated with Havrix 720. The formula that was used to calculate x (in periods of 4 weeks) was derived from Eq. (5):

$$x = (m-n) * \frac{\log_{10}(20) - \log_{10}(titer_{76})}{\log_{10}(1-\delta)} + n \quad (6)$$

with $m = 32$ and $n = 19$
x = a number of intervals of 4 weeks.

Figure 2 shows the proportion of subjects for each study group that is estimated to maintain antibody levels ≥ 20 mIU/ml over time. Ten years after completion of the full vaccination course, about 53% of subjects are estimated to have antibody levels ≥ 20 mIU/ml, independent of the type of vaccine used. At 15 years after completion of the full course, these levels will be maintained by about 34% of vaccinees.

In our analyses, both Avaxim and Havrix 720 show the same long-term profile, with 50% of the subjects being expected to have at least 20 mIU/ml anti-HAV for about 10.3 years, independent of the vaccine type used.

Figure 3 shows the antibody decrease for the subject at the 25th, 50th, or 75th percentile (i.e., the best of the 25%, 50%, or 75% worst responders, respectively) at every point in time, and reveals the same trends for both vaccines. Avaxim and Havrix 720 show the same long-term antibody kinetic profiles for the subjects. Antibody levels ≥ 20 mIU/ml are estimated to last on average for at least 10 years after completion of the vaccination course.

Comparison Between Predicted and Observed Values for the Year 3 Post-Booster Follow-Up

The model-based calculations, as described above, were performed before the third annual follow-up blood sampling after the administration of the booster dose (week 180) was done. Therefore, it was decided to use the data from week 180 to test the robustness of the models described herein.

For the Avaxim group, the calculated value for week 180 was 509 mIU/ml (GMT method) and also 509 mIU/ml (95% CI: 170–1,524 mIU/ml) based on the individual data. For Havrix 720, the calculated GMT based on the GMT method was 422 mIU/ml and based on the individual data it was again identical: 422 mIU/ml (95% CI: 130–1,370 mIU/ml). The observed values in the cohort that participated in the follow-up were as follows: 751 mIU/ml (95% CI: 616–916 mIU/ml) for Avaxim, and 602 mIU/ml (95% CI: 501–724 mIU/ml) for Havrix 720.

DISCUSSION

These results confirm the published estimates of the persistence over time of anti-HAV antibodies after vac-

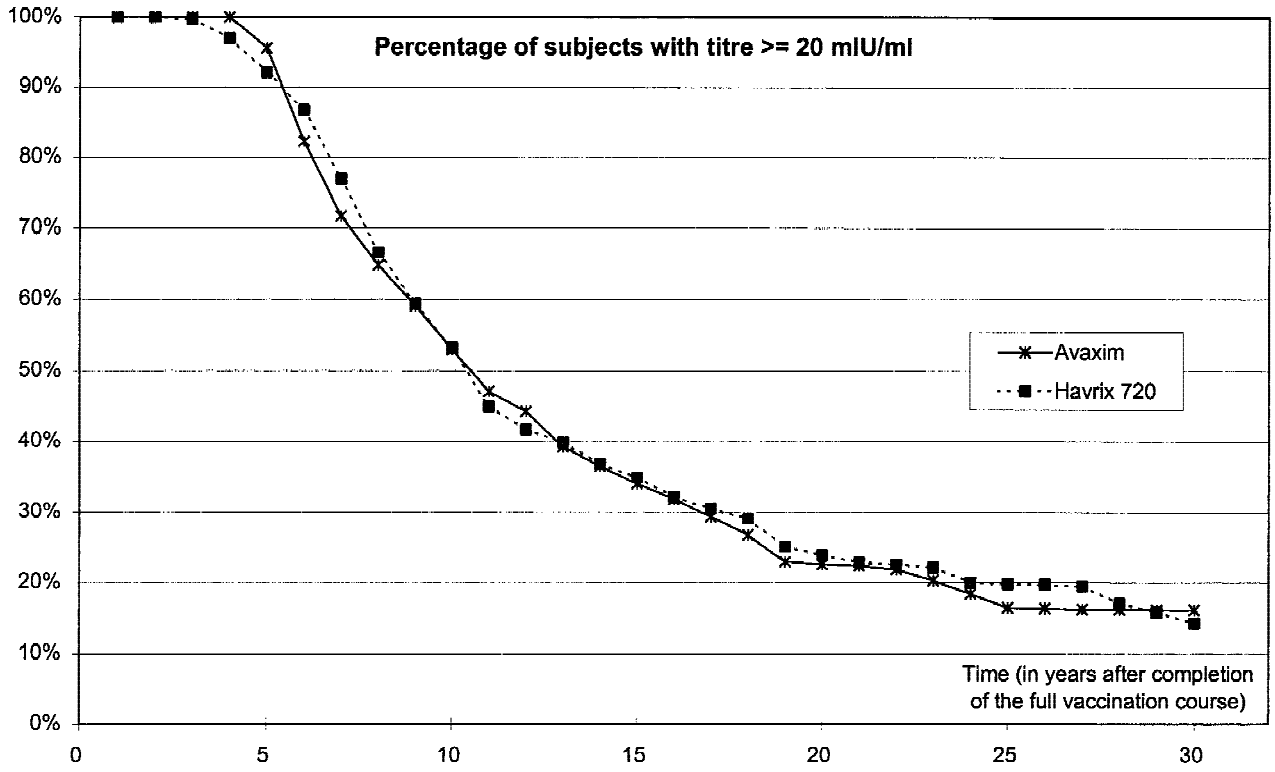

Fig. 2. Estimated percentage of subjects given either Avaxim (0–6 months) or Havrix 720 (0–1–6 months) who will have at least the seroconversion level of anti-hepatitis A virus (anti-HAV) (≥ 20 mIU/ml).

cination. For Havrix 720, Maiwald et al. [1997] reported an antibody persistence ≥ 20 mIU/ml for at least 15 years and Van Damme et al. [1994] reported at least 20 years persistence ≥ 20 mIU/ml. Wiedermann et al. [1997] estimated hepatitis A antibody titres ≥ 10 mIU/ml to persist for at least 20 years, for different doses of Havrix. Since the start of this clinical trial, Havrix 1440 has replaced Havrix 720 for adult vaccination. However, we did not apply the data from Havrix 1440, because these data were not available at the time of the start of this study. More recently, it was shown that > 99% of subjects vaccinated with Havrix 1440 still had an anti-HAV titre ≥ 20 mIU/ml 4 years after their first dose and the antibody kinetics looked similar to the one obtained with the 720 El.U vaccine [Van Damme et al., 1998]. Wiens et al. [1996] reported anti-HAV antibodies remained ≥ 10 mIU/ml for many years, and probably decades, after vaccination with different doses of Vaqta (Merck, USA). With a virosomal hepatitis A vaccine, antibody levels ≥ 20 mIU/ml were estimated to last for 8–12.5 years [Bovier et al., 1997; Lea and Balfour, 1997].

Both methods of calculating the mean annual slow decrease rate and the mean duration of antibody persistence led to similar findings. Using GMT values as the basis for calculation, it is possible to estimate when the GMT of a group of vaccinees will reach a given value. The result is thus to be interpreted as the number of years after the first vaccine dose that the group of vaccinees, as an entity, will maintain a level of antibodies ≥ 20 mIU/ml (in terms of GMT). When the calculations are based on individual data, it is noteworthy that the annual slow decrease rate and therefore also the duration of antibody persistence lead to higher individual variability: each individual responds in a different way. Nevertheless, the mean annual decrease rate, with its 95% CI, is comparable to the value that is found with the GMT-based analysis. In contrast, the GMT-based method has a tendency to underestimate the mean duration of antibody persistence compared with the values calculated by the method based on the individual data. Nevertheless, the results of both methods appeared to be equivalent. The GMT method is easier to apply than the method based on individual data. However, the advantage of the latter method is the possibility to calculate confidence limits for the predicted values and to make estimates of the percentage of subjects having a certain level of antibody titres at a certain time.

When the two different methods of mathematical modelling are compared with one another, each seems to have specific advantages. Starting from individual data, one might be able to give a better individual prediction, as far as an individual antibody titre is known for at least two points in time. This implies individual antibody testing after vaccination, which might be useful in certain specific situations, but which is not recommended routinely from a public health point of view [Centers for Disease Control and Prevention, 1996]. With the GMT approach, one is bound to make a more

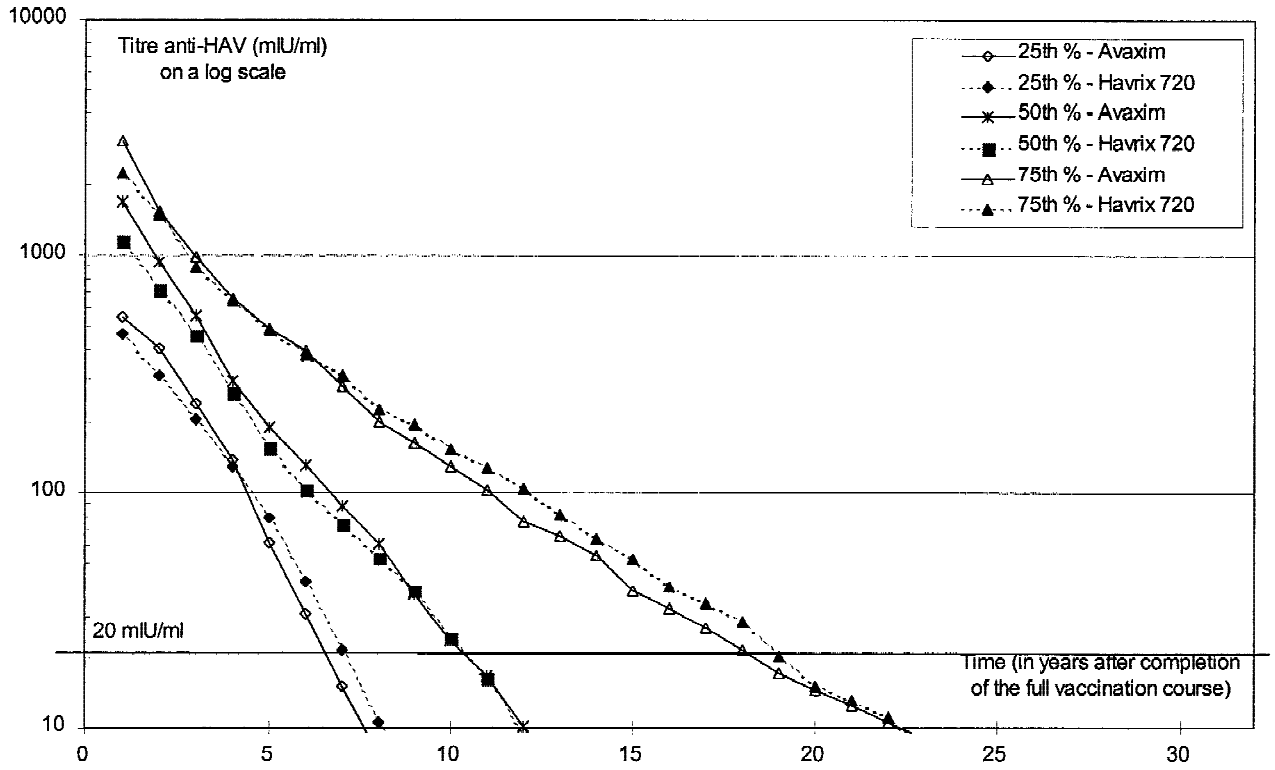

Fig. 3. Calculated loss of anti-hepatitis A virus (anti-HAV) antibodies over time in subjects given either Avaxim (0–6 months) or Havrix 720 (0–1–6 months) at the 25th, 50th and 75th percentile. Plotted in green: Havrix 720; Plotted in blue: Avaxim. Left: 25th percentile, centre: 50th percentile, right: 75th percentile.

general statement about the group of vaccinees as such, which seems easier for public health issues.

During the first trial visits (after the first vaccination), the antibody response to vaccination was influenced significantly by gender and vaccine type [Goilav et al., 1995]. Subjects receiving Avaxim had higher antibody levels than those receiving Havrix 720 at each point in time. It can be questioned whether the latter observation has any clinical relevance. However, the influence of these two factors diminished over time and seemed to disappear in the long run. In terms of long-term persistence of antibodies, Avaxim and Havrix 720 showed similar results. For hepatitis B vaccine, gender, age, weight, and smoking habits of vaccinees are factors with a well-known influence on immunological response after vaccination [Hollinger, 1989]. For hepatitis A, Maiwald et al. [1997] found a significant influence of the gender, but not of age and weight. Reuman et al. [1997], however, showed an influence of age and body weight of subjects vaccinated with another inactivated hepatitis A vaccine. In the present study, age as well as weight showed a slightly negative correlation with the anti-HAV antibody titres ($r = -0.35$ was the strongest to be found). The interaction between weight and antibody titres became negative from week 24 further onwards. The influence of age on antibody titres was statistically significant at all points in time. The analysis of covariance showed that the covariates age and weight were significant in the model. However, these covariates did not account for a large proportion of the variance in antibody titres (R^2 was never higher than 0.16). Other variables that may influence the immune response (e.g., smoking behaviour, genetic factors) were not assessed in this trial. These variables might also explain some of the differences that were established in this trial.

It is noteworthy that if the exclusion criteria for the current analysis of these data had been set differently, i.e., only including in the analysis those subjects who respected the exact timing specified in the protocol (at all points in time) the number of subjects in the analysis would have been reduced dramatically and some of the differences that are described in this report would no longer hold. For instance, Avaxim would not induce a higher GMT at all points in time and the annual slow decrease rate δ would be lower (and thus the expected number of years before the anti-HAV level would reach 20 mIU/ml would be higher). One might even wonder if subjects who participate correctly in a clinical trial at every point in time would have a profile that sets them apart from other subjects. They may be more concerned about their health and thus form a "healthier" group with a specific immunological behaviour, creating a bias for the study results that seems difficult to quantify. This could be an interesting topic to be studied in other long-term follow-up studies in the future.

The observed GMT values at year 3 were within the 95% confidence limits of the predicted values. How-

ever, the predicted GMT values were below the 95% confidence limits of the observed year 3 GMTs. This finding could be due to the fact that 31 subjects in the Avaxim group and 28 subjects in the Havrix 720 group were lost to follow-up at year 3. This loss of subjects means that the observed GMTs are calculated from a different population than the population that was included in the mathematical modelling.

If, however, the noncompliance of these subjects would have no influence on the observed GMT, then our methods of calculation seem rather conservative. Indeed, the predicted GMT values at year 3 are an underestimate of the observed GMTs, implying that the mean annual decline rate, as it is described in this paper, is overestimated. Consequently, the predicted interval of persistence of anti-HAV antibodies is probably underestimated, and it is acceptable to conclude that antibodies would persist, on average, for at least 10 years after the full course of vaccination. Furthermore, all the results of the calculations can be regarded as conservative estimates of the long-term persistence of anti-HAV antibodies.

To be able to calculate the annual decay rate and the duration of antibody persistence more accurately, further follow-up data are needed to substantiate the existing models. Those new data could be used to check whether the expected and the measured titres are alike and to improve the algorithm on which these models are based.

In general, it is concluded that the Avaxim and the Havrix 720 groups will maintain antibody levels $\geq$ 20 mIU/ml on average for at least 10 years after the completion of the full vaccination course. Ten years after the full course, about 53% of subjects are estimated to have antibody levels $\geq$ 20 mIU/ml, and at 15 years after completion, about 34% of vaccinees will still maintain antibody levels $\geq$ 20 mIU/ml.

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